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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BAUM, STUART F	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 10/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/058,825	SCOTT, RODERICK JOHN	
	Examiner	Art Unit	
	Stuart F. Baum	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-22 and 40-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-22 and 40-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/6/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *NCBI Accession Numbers*.

DETAILED ACTION

1. Claims 20-22 and 40-60 are pending.

2. Applicant's election with traverse of Group XI, claims 20-22 in the reply filed on 7/28/2004 is acknowledged. The traversal is on the ground(s) that the present claims do not present such a serious burden on the Examiner as to make restriction proper.
This is not found persuasive because while the search of the prior art for one group may overlap with that of another, they are not co-extensive of each other and thus would be a burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-19 and 23-39 have been canceled.

Claims 40-60 have been newly added and are drawn to the subject matter of Group XI.

3. Claims 20-22 and 40-60 are examined in the present office action.

Claim Objection

4. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 40-60 have been renumbered 62-82. Claims 40-61, (claims originally filed as 36-57) that were presented in the amendment filed 4/26/2004 are still pending

and have been withdrawn from consideration for being drawn to a non-elected invention. Applicant is request to cancel said claims in the next filed amendment.

5. Claims 20-22 and renumbered claims 62-82 are examined in the present office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 20-22 and 62-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection includes dependent claims.

The term "reduces" in claim 20 is a relative term which renders the claim indefinite. The term "reduces" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 22, 62-63, 69-70, 74-75, are indefinite in the recitation "Met1". The sole designation of a nucleic acid sequence by "Met1" is arbitrary and creates ambiguity in the claims. For example, the nucleic acid sequence in this application could be designated by some other arbitrary means, or the assignment of said name could be arbitrarily changed to designate a different nucleic acid sequence. If either event occurs, one's ability to determine the metes and bounds of the claim would be impaired. See *In re Hammack*, 427 F .2d 1378, 1382; 166 USPQ 204, 208 (CCPA 1970). Amendment of the claim to refer to a specific SEQ ID NO would obviate this rejection.

Written Description

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 20-22 and 62-82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of modifying endosperm comprising introducing into a plant a nucleic acid molecule operably linked to a promoter wherein transcription of the nucleic acid molecule reduces the degree of DNA methylation of nucleic acids in the plant by down-regulating one or more DNA methylating enzymes present in the plant, or wherein the nucleic acid molecule is operably linked to a promoter in antisense or sense orientation, or wherein the nucleic acid molecule in sense orientation is a full or partial sense copy, or wherein the nucleic acid molecule is antisense to Met1, or wherein the nucleic acid molecule is antisense to Z. mays or B. napus sequence orthologous to Met1, or wherein the transcription of the nucleic acid molecule down-regulates any DNA methylating enzyme, or wherein the nucleic acid molecule produces a ribozyme transcription product, or wherein the ribozyme transcription product is to a Z. mays or B. napus sequence orthologous to Met1.

Applicant has provided a list of examples of methylating enzymes from Arabidopsis, including accession numbers; Methylase 1 (NCBI Acc no. C10692, September 1996), Methylase 1-like gene (NCBI Acc. No. Z97335 June, 1999), Methylase 2 (NCBI Acc. No. AL021711, March, 2000), and Chromomethylase (NCBI Acc. No. U53501, May 1996) (page 18, lines 17-21, NCBI accession numbers included).

The Office contends that Applicant's methylase 1 example, acc. Nr. C10692 is to an unidentified protein from *Caenorhabditis elegans*, and the last three accession numbers (i.e., Z97335, AL021711, and U53501) are for a contig fragment comprising 200,576 nucleotide bases that does not specify a "Methylase 1-like" gene or protein, a Bac clone comprising 119,112 nucleotide bases that does not specify a "Methylase 2" gene or protein and a cosmid comprising 37570 nucleotide bases that does not specify a "Chromomethylase" gene or protein, respectively. Applicant has not specifically identified the sequence that encodes any methylating enzymes, especially a nucleic acid encoding a Met1. Applicant has not disclosed a correlation between a nucleic acid structure and a function. Applicant has not disclosed any nucleic acid molecule that can be used to down regulate one or more DNA methylating enzymes. Applicant has only disclosed that a Met1 sequence was isolated from Arabidopsis (page 30, Example 3) but Applicant does not disclose the sequence nor does Applicant disclose any generic Met1 sequence nor any Z. mays or B. napus sequence orthologous to Met1. Applicant has not disclosed any ribozyme sequence or any ribozyme to a Z. mays or B. napus sequence orthologous to Met1.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court

stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. The court goes on to say, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Applicants fail to describe a representative number of polynucleotide sequences encoding a Met1 protein falling within the scope of the claimed genus of polynucleotides. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of polynucleotides. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for the Met1 protein, it remains unclear what features identify any Arabidopsis Met1 protein or a Z. mays or B. napus Met1 orthologoue. Since the genus of Met1 proteins has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

Scope of Enablement

8. Claims 20-22 and 62-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for increasing the amount of endosperm in a seed comprising a construct comprising a MET1 cDNA operably linked to any promoter that

expresses in the male or female gametophyte in antisense orientation, wherein the MET1 cDNA is isolated by RT-PCR from Arabidopsis using the primers MET1F of SEQ ID NO:5 and MET1R of SEQ ID NO:6 and plant transformation therewith, does not reasonably provide enablement for claims broadly drawn to a method of modifying the endosperm comprising down-regulating any DNA methylating enzyme using any nucleic acid sequence, wherein the nucleic acid sequence encodes any Met1 protein or encodes a Z. mays or B. napus Met1 orthologue, or any ribozyme or a ribozyme to a Z. mays or B. napus Met1 orthologue, or wherein the nucleic acid is a partial or full length sense copy encoding a DNA methylating enzyme wherein the methylating enzyme is a Z. mays or B. napus orthologue to Met1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are drawn to a method of modifying endosperm comprising introducing into a plant a nucleic acid molecule operably linked to a promoter wherein transcription of the nucleic acid molecule reduces the degree of DNA methylation of nucleic acids in the plant by down-

regulating one or more DNA methylating enzymes present in the plant, or wherein the nucleic acid molecule is operably linked to a promoter in antisense or sense orientation, or wherein the nucleic acid molecule in sense orientation is a full or partial sense copy, or wherein the nucleic acid molecule is antisense to Met1, or wherein the nucleic acid molecule is antisense to Z. mays or B. napus sequence orthologous to Met1, or wherein the transcription of the nucleic acid molecule down-regulates any DNA methylating enzyme, or wherein the nucleic acid molecule produces a ribozyme transcription product, or wherein the ribozyme transcription product is to a Z. mays or B. napus sequence orthologous to Met1.

Applicant discloses subcloning the MET1 cDNA, which is 4.7kb long, isolated by RT-PCR from an Arabidopsis cDNA library using the MET1F primer of SEQ ID NO:5 and MET1R primer of SEQ ID NO:6, subcloned into a vector comprising the AGL5 or AP3 promoter in antisense orientation (page 30, Example 3) and transformation into Arabidopsis (page 31, Example 4) or into Brassica campestris and Brassica oleraceae (page 33, Example 5). The resultant plant exhibited seeds with increased weight and endosperm.

The state-of-the-art teaches down-regulating methylating genes produces unpredictable results. Jacobsen et al (2000, Current Biology 10:179-186) teach transforming *Arabidopsis* with a nucleic acid encoding the MET1 protein operably linked to a promoter in antisense orientation caused a decrease in methylation by 80%-90%. Jacobsen et al disclose that "Surprisingly, this work showed that the floral development gene *SUPERMAN* was ectopically hypermethylated and silenced" (page 180, left column, 1st full paragraph).

Applicant's claims read on any sequence or any Met1 sequence from any plant or Met1 from Z. mays or B. napus but Applicant has only disclosed primer sequences to be used for

isolating an Arabidopsis MET1 cDNA. Applicant has not disclosed how one makes or isolates any of the other sequences that are encompassed by Applicants' broad claims. Applicant has not taught which regions of the respective polynucleotides can be used to amplify any of said polynucleotides or which regions can be used as a probe to isolate any of said polynucleotide sequences.

Using degenerate primers to amplify a target sequence does not always produce expected results. The state-of-the-art teaches DNA fragments do not always hybridize with the expected complementary DNA. Fourgoux-Nicol et al (1999, Plant Molecular Biology 40 :857-872) teach the isolation of a 674bp fragment using a 497bp probe incorporating stringent hybridization conditions comprising three consecutive 30 minute rinses in 2X, 1X and 0.1X SSC with 0.1% SDS at 65^0C (page 859, left column, 2^{nd} paragraph). Fourgoux-Nicol et al also teach that the probe and isolated DNA fragment exhibited a number of sequence differences comprising a 99bp insertion and a single nucleotide gap, while the DNA fragment contained 2 single nucleotide gaps and together the fragments contained 27 nucleotide mismatches. Taking into account the insertions, gaps and mismatches, the longest stretch of contiguous nucleotides to which the probe could hybridize consisted of 93bp of DNA (page 862, Figure 2).

Using DNA sequences to reduce expression of the endogenous corresponding gene through the mechanism of sense suppression produces unpredictable results. Gutterson (1995, HortScience 30(5):964-966) teaches that the chrysanthemum and petunia chalcone sythase (CHS) genes are 70% identical to each other, and that transforming petunia plants with the chrysanthemum CHS gene did not co-suppress the endogenous petunia CHS gene (page 965, left

column, second paragraph). Gutterson reports similar data using another petunia gene in the anthocyanin pathway.

The state-of-the-art teaches that antisense molecules that exhibit less than 100% sequence identity to the target sequence produce unexpected results. Emery et al (2003, Current Biology 13:1768-1774) disclose experiments in which a target sequence of a micro-RNA was changed by two base-pairs. The altered base-pairs caused the complementary micro-RNA not to bind to the target sequence, which subsequently led to an increased expression of the target sequence's encoded protein (page 1769, right column, 2nd full paragraph).

Using ribozymes to down regulate a particular gene produces unpredictable results. Mazzolini et al (1992, Plant Molecular Biology 20:715-731) teach a hammerhead ribozyme designed against the mRNA coding for the GUS enzyme was constructed and co-transformed into protoplast along with the GUS reporter gene. Mazzolini et al report "Although the GUS levels in protoplasts in the presence of the ribozyme were consistently found to be lower than those of the controls over three independent experiments, the observed differences in GUS activity were never statistically different" (page 722, bottom, right column and page 723, top left column).

In the absence of guidance, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified sequences, either by using degenerate primers to amplify the respective sequences or by using non-disclosed fragments the MET1 cDNA as probes or by designing primers to undisclosed regions of the MET1 cDNA and isolating or amplifying fragments, subcloning the fragments, producing expression vectors and transforming plants therewith, in order to identify those, if any, that when

over-expressed are able to down-regulate the endogenous DNA methylating enzyme and reduce the amount of methylated DNA and produce seeds with increased weight and endosperm.

Therefore, given the breadth of the claims; the lack of guidance and examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to practice the claimed invention, and therefore the invention is not enabled.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 20-22, 64-65, 77-79 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Ronemus et al (1996, Science 273 (2 August):654-657).

The claims are drawn to a method for the production of modified endosperm comprising introducing a nucleic acid molecule operably linked to a promoter, into a plant wherein the transcription product reduces the degree of DNA methylation of nucleic acids in the plant by down-regulating one or more DNA methylating enzymes present in the plant, wherein the nucleic acid molecule is operably linked to said promoter in antisense orientation, wherein the transcription product comprises an antisense nucleic acid to Met1, wherein the plant is a dicotyledonous plant, wherein the transcription product down-regulates one DNA methylating enzyme, or wherein the promoter directs expression in female gametic cells.

Ronemus et al disclose an antisense construct comprising a 4.3kb MET1 cDNA from *Arabidopsis* in antisense orientation operably linked to the CaMV 35S promoter transformed into Arabidopsis, to inhibit the endogenous expression of the MET1 gene (page 654, middle column). Ronemus et al disclosed the antisense construct resulted in substantial demethylation

of DNA (page 655, left column, bottom of 1st paragraph). Given that the method steps of Ronemus et al are the same as Applicant's and given that the antisense construct of Ronemus et al would express in the female and male gametes because the 35S promoter is a constitutive promoter, it would be inherent that the method of Ronemus et al would have the same effect on the endosperm as Applicant's method, and as such, Ronemus et al anticipate the claimed invention. See *Integra LifeSciences I Ltd. V. Merck KGaA* 50 USPQ2d 1846, 1850 (DC SCalif 1999), which teaches that where the prior art teaches all of the required steps to practice the claimed method and no additional manipulation is required to produce the claimed result, then the prior art anticipates the claimed method.

10. Claims 62-63, 66-76 and 80 are free of the prior art given the failure of the prior art to teach or reasonably suggest a method for the production of modified endosperm comprising transforming a plant with a nucleic acid encoding a Z. mays or B. napus polypeptide orthologous to Met1, wherein the nucleic acid is in antisense orientaiton or in sense orientation and acts to co-suppress the endogenous sequence or wherein said sequence is a partial or full sequence, or a nucleic acid encoding a ribozyme to a Z. mays or B. napus sequence orthologous to Met1.

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart F. Baum whose telephone number is 571-272-0792. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Stuart F. Baum Ph.D.
Patent Examiner
Art Unit 1638
October 12, 2004